AR201-14133

PMSurana@celanese.com on 12/17/2002 12:12:41 PM

To: oppt.ncic@epamail.epa.gov
cc:

Subject: HPV Program

Attached with this e-mail is a cover letter, test plan and robust summaries for 1,3-Butanediol (CAS# 107-88-0)
<<107-88-0-CL.pdf>> <<107-88-0-RS.pdf>> <<107-88-0-TP.pdf>>

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107-88-0-CL.pdf


107-88-0-RS.pdf


107-88-0-TP.pdf

December 17, 2002

To: oppt.ncic@epa.gov

Subject: HPV Program

Re: Test plan and Robust Summaries for 1,3- Butanediol

Dear Administrator Whitman:

Celanese Ltd. (Registration number is pleased to submit the test plan along with robust summaries for the chemical **1,3-Butanediol, CAS# 107-88-0** under the U.S. Environmental Protection Agency's (EPA) High Production Volume Chemical Challenge Program. Celanese understands there will be a 120-day review period for the test plan and that all comments generated by, or provided to, EPA will be forwarded to Celanese Ltd. for consideration.

The submission includes one electronic copy of the test plan and the robust summaries in .pdf format.

Please feel free to contact me with any questions regarding the test plan or robust summaries by phone at 972-443-4836 or by e-mail at pmsurana@celanese .com.

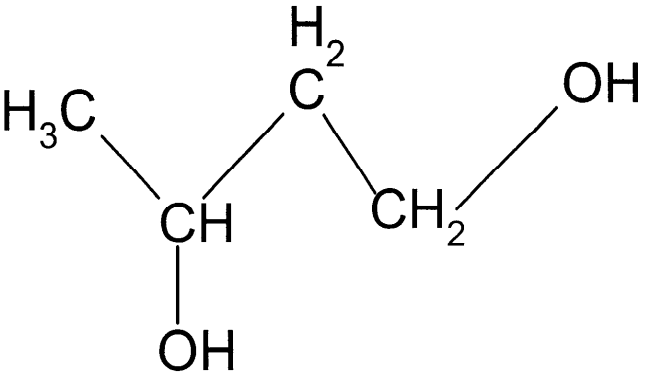
Sincerely,

Prakash Surana, Ph.D.
Product Stewardship Coordinator
Celanese Ltd.

AR201-14133A

1,3-Butanediol

CAS Number 107-88-0



USEPA HPV Challenge Program Submission

December 17, 2002

Submitted by:

Celanese Limited

Prepared by:
Toxicology and Regulatory Affairs
1201 Anise Court
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Table of Contents

Executive Overview

1,3-Butanediol is a diol used as a chemical intermediate in the manufacture of polyester plasticizers and other products. It finds some use as a solvent for flavorings and as a humectant in pet foods, tobacco and cosmetics. The U.S. FDA sanctions the use of 1,3-Butanediol as a food additive in several direct and indirect applications. Use in cosmetics has been reviewed by the Cosmetic Ingredient Review, who published a report in 1985 concluding that 1,3-Butanediol was safe as presently used in cosmetics. Industrial exposures by the inhalation and dermal routes are considered minimal as the industrial uses are thought to be almost exclusively closed systems and the material has a relatively low vapor pressure.

Physicochemical properties of 1,3-Butanediol are well established and indicate that it is a slightly-volatile liquid with high water solubility. The value of the octanol-water partition coefficient suggests that 1,3-Butanediol will partition preferentially into water and has little potential for bioaccumulation.

The estimated half-life of 1,3-Butanediol vapor in air, due to indirect photolysis, is approximately 9 hours. The material is considered stable to hydrolysis in water. It was found to be readily biodegradable by the OECD criteria. Fugacity calculations indicate preferential distribution to water and soil. Toxicity to aquatic species was determined using direct investigation and SAR modeling. The results indicate a low hazard potential for fish, aquatic invertebrates and aquatic plants.

Studies of 1,3-Butanediol metabolism show that it is readily converted by mammals to β-hydroxybutyraldehyde, which is in turn, rapidly oxidized to β-hydroxybutyrate. Subsequent metabolic steps lead to acetoacetate and acetyl CoA, followed by entry of acetyl CoA into the tricarboxylic acid cycle to produce carbon dioxide and reducing equivalents that are converted to ATP by the electron transport chain. In addition, acetyl CoA is a central intermediate metabolite in lipid biosynthesis and can be converted to sterols and fatty acids.

Acute toxicity is minimal by the oral and inhalation routes, and repeated-dose administration of high doses to experimental animals and humans does not produce adverse effects until the amount ingested becomes a significant contributor to the individual's caloric requirement. Even then, the observed effects are limited to minor reduction in body weight gains and alterations in serum glucose, ketone bodies and fatty acid synthesis resulting from the metabolism of 1,3-Butanediol as a nutrient. Multigenerational and developmental toxicity studies produced no remarkable findings. Genotoxicity studies indicate lack of genototoxic effects and chronic studies did not show any carcinogenic activity.

No additional toxicity testing is recommended for this well-studied and essentially non-toxic material.

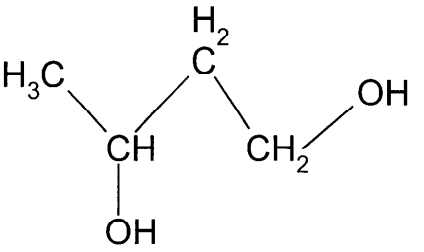
Testing Plan and Rationale

Testing Plan in Tabular Format

CAS Number 107-88-0 1,3-Butanediol	Information Available?	OECD Study ?	GLP Study?	Other Information ?	Estimation Method?	Acceptable?	Testing Recommended?	
HPV Endpoint								
Physical Chemical								
Melting Point	Y	N	N	Y	N	Y	N	
Boiling Point	Y	N	N	Y	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	N	N	N	Y	Y	N	
Water Solubility	Y	N	N	N	N	Y	N	
Environmental & Fate								
Photo-Degradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	Y	Y	Y	N	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	Y	Y	N	Y	N	
Ecotoxicity								
96-Hour Fish	Y	N	N	N	Y	Y	N	
48-Hour Invertebrate	Y	N	N	N	Y	Y	N	
72-Hour Algae	Y	Y	Y	N	N	Y	N	
Toxicity								
Acute	Y	N	N	Y	N	Y	N	
Repeated Dose	Y	N	N	Y	N	Y	N	
Genetic Toxicology *in vitro*	Y	N	N	Y	N	Y	N	
Genetic Toxicology *in vivo*	Y	N	N	Y	N	Y	N	
Reproductive	Y	N	N	Y	N	Y	N	
Developmental	Y	N	N	Y	N	Y	N	

Introduction

1,3-Butanediol, CAS Number 107-88-0 is a four carbon glycol with a sweet flavor and a bitter aftertaste (1). It is a clear, viscous, low-volatility liquid that is miscible with water and most polar organic solvents but only slightly soluble in ether. It is insoluble in aliphatic hydrocarbons, benzene, and carbon tetrachloride. Its most extensive use is as an intermediate in the manufacture of polyester plasticizers and other chemical products. It finds some use as a solvent and humectant; the structure is shown below:



1,3-Butanediol is also known as:

- 1,3-Butylene Glycol
- Beta-Butylene Glycol
- Butane-1,3-Diol
- 1,3-Dihydroxybutane
- 1-Methyl-1,3-Propanediol
- Methyltrimethylene Glycol

The chemical and physical properties of 1,3-Butanediol make it a unique solvent for certain applications and a useful chemical intermediate. The most extensive use for 1,3-Butanediol is as an intermediate in manufacture of certain polyester plasticizers (2). These plasticizers are valuable because of their compatibility with a broad range of polymers and the resultant stability of the plasticized material. This use currently accounts for about half the 1,3-Butanediol production.

Another important application is in the manufacture of structural materials for boats, custom moldings, and sheets and boards for construction applications. 1,3-Butanediol imparts resistance to weathering plus flexibility and impact resistance. It is also used in the manufacture of saturated polyesters for polyurethane coatings, where the glycol imparts greater flexibility to the polyester molecule. This application currently accounts for about 30% of the 1,3-Butanediol produced and includes coatings, foams and elastomer production. About one third of this (10% of the total production) goes into multifunctional monomer production for radiation-cured coatings.

1,3-Butanediol is an outstanding humectant (3), especially when compared with other glycol series humectants. It has the capability to acquire and maintain atmospheric moisture at nearly constant levels in the important 20-25% humidity range (4). 1,3-Butanediol is a highly effective humectant in pet foods, tobacco and cosmetic formulations. In cosmetic formulations it inhibits the drying out of cosmetics and the crystallization of insoluble components in cosmetic vehicles. Products employing this chemical are more resistant to high humidity. It is used as a humectant in cosmetics, especially in hair sprays and setting lotions (5). Currently about 10% of total U.S. 1,3-Butanediol production goes into personal-care products.

Miscellaneous end-use areas for 1,3-Butylene Glycol are in surfactants, inks, solvents for natural and synthetic flavorings and coupling agents in cellophane (4). These miscellaneous uses altogether account for a few percent of the 1,3-Butanediol usages in the United States.

Exposure in industrial applications is limited by process controls and protective equipment; however, there is no occupational exposure level set by any governmental agency. Manufacture of this material is in a closed system and the only significant exposure is in the open-cap loading of rail cars and tank cars. Workers doing the loading wear appropriate personal protective equipment and stay in the area where vapors are released only a short time. Use as a humectant in consumer products results in a low-level of inhalation exposure limited by the low volatility of this material. In some cosmetic applications, such as eye shadow or makeup foundations, use will result in dermal exposure. Extensive animal studies have shown that it is of low toxicity and actually serves as a mammalian nutrient.

Several fate and toxicity studies have been conducted on 1,3-Butanediol. These studies are briefly reviewed in this testing rationale document, which describes how they meet the SIDS (Screening Information Data Set) endpoints of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge (HPV) program. Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries or given as shorter summaries using the IUCLID format. The available data set satisfactorily fulfills the data requirements for the EPA HPV Program. Although all endpoints are not filled by experimental data, the estimation of some endpoints from SAR relationships is satisfactory for this low-hazard member of the aliphatic polyol family and encouraged to avoid unnecessary animal usage.

Approved Food Applications

The U.S.FDA and the Joint FAO/WHO Expert Committee on Food Additives have both evaluated 1,3-Butanediol for human dietary intake. JECFA has set an "Estimate of acceptable daily intake for man" of 0 to 4 mg/kg-body weight.

The FDA covers 1,3-Butanediol in several sections of the Code of Federal Regulations sanctioning both direct and indirect food additive applications.

FDA Sanctioned Food Application of 1,3-Butanediol		
21CFR Section	**Type Additive**	**Application**
172.712	Direct	In sausage casings as formulation aid or processing aid
173.220	Direct	Solvent for flavorings
175.105	Indirect	Component of food-contact adhesives
175.320	Indirect	Component of coating for food-contact polyolefin films.
177.1200	Indirect	Component of cellophane used in food-contact
177.1210	Indirect	Component of sealing gaskets for food-contact
177.1680	Indirect	Monomer for food-contact polyurethanes
177.2420	Indirect	Monomer for food-contact polyesters
178.2010	Indirect	Antioxidant and/or stabilizer for food-contact polymers

Cosmetic Applications

1,3-Butanediol is currently used in many personal care products. Its safety for these applications was reviewed by the Cosmetic Ingredient Review of the Cosmetic, Toiletry and Fragrance Association, which published a report in 1985 (6) concluding that 1,3-Butanediol was safe as presently used in cosmetics.

Physical-chemical Data

Physical-chemical data for 1,3-Butanediol are available from the literature and manufacturer's information.

Melting Point	-77° C (7)
Boiling Point	207.5 deg C @ 1013 hPa (7)
Vapor Pressure	0.027 hPa @ 20° C (8) 0.08 hPa @ 20° C (9)
Partition Coefficient	Log $K_{o/w}$ = -0.29 (10)
Water Solubility	Soluble in all proportions (3)

These properties indicate that 1,3-Butanediol is a slightly volatile liquid with high water solubility. The value of the partition coefficient suggests that 1,3-Butanediol will partition preferentially into water and has little potential for bioaccumulation.

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints.

Environmental Fate and Pathways

Biodegradation potential was recently determined using a modified Sturm Test according to OECD Guideline 301B. In this carbon dioxide evolution test, approximately 80% of the theoretical carbon dioxide production was achieved in 28 days using non-adapted domestic sludge (11). Thus, 1,3-Butanediol is considered readily biodegradable by the OECD criteria.

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. The program produced a estimated rate constant of 14.2329 E-12 cm3/molecule-sec. Using the default atmospheric hydroxyl radical concentration in APOWIN and the estimated rate constant for reaction of 1,3-Butanediol with hydroxyl radical, the estimated half-life of 1,3-Butanediol vapor in air is approximately 9 hours (see accompanying robust summary).

Water stability has not been quantitatively determined for 1,3-Butanediol. Quantitative stability determinations are considered unnecessary for compounds containing only non-hydrolysable groups, as the SIDS manual states that consideration should be given to using an estimation method. There is no evidence available that 1,3-Butanediol is unstable in water and as it has no hydrolysable groups, the half-life in water is estimated with high confidence at greater than one year (12).

Theoretical Distribution (Fugacity) of 1,3-Butanediol in the environment was estimated using the MacKay model with standard defaults in EPIWIN v 3.05 but using the more conservative vapor pressure of 0.06 mm Hg (13). The results for distribution using a model calculated Ko/c (adsorption coefficient based on organic carbon content) of 0.21 are:

- Air 2.96 %
- Water 49.7 %
- Soil 47.3 %
- Sediment 0.074 %

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints.

Ecotoxicity

A recent GLP guideline (OECD 201) study of algal inhibition using measured concentrations of 1,3-Butanediol is available demonstrating low hazard to green algae after 72 hours of exposure (14). No studies of fish or invertebrate aquatic toxicology were found. EPIWIN estimates, using the neutral organic model are given in the table below.

Aquatic Toxicity 1,3-Butanediol	
Fish, 96 hour LC_{50}	8984 mg/L*
Daphnia, 48 hour EC_{50}	7344 mg/L*
Algae, 72 hour EC_{50}	> 1070 mg/L (14)

* Estimated using ECOSAR (15)

These estimates are supported by the very high fish and daphnia EC50 values for the similar compounds 1,2-propanediol (16), 1,4-butanediol (17), 1,2-butanediol (18) and 1,2-ethanediol (19) that have been experimentally determined to be in the same range as that predicted for 1,3-Butanediol using the ECOSAR modeling program and SAR relationship contained therein. The SAR "neutral organics" relationship is verified to be a reasonably accurate predictor of actual toxicity by the predictions verses measured values for these surrogate compounds as shown below. Although the measured daphnia value for 1,4-butanediol is lower that the predicted value by almost an order of magnitude, the measured toxicity of 1,4-butanediol to daphnids is still in a range not to be of environmental concern.

Compound	Fish LC_{50} (mg/L)		Daphnids EC_{50} (mg/L)	
	ECOSAR	Measured	ECOSAR	Measured
1,4-Butanediol	8,100	>10,000	7,500	813
1,2-Butanediol	9,500	>1000	8,700	>1000
1,2-Propanediol	23,150	23,000	20,470	34,400
1,2-Ethanediol	47,000	27,540-49,300	40,260	46,300

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints without unnecessary aquatic animal usage. Although definitive experimental data are not available for fish and daphnia toxicity, the ECOSAR model predicts low hazard. The algae data prediction partially validates the ECOSAR modeling for this material and the low hazard of most other simple glycols also substantiates the estimates. As the estimates indicate EC50 values several fold greater than the usual limits of concentration in the standard OECD protocols (100-1000 mg/L), there is a high degree of confidence in the estimation of the acute EC50 values for fish and daphnids at > 1000 mg/L.

Health Effects

Several studies have been conducted to determine the potential health effects of 1,3-Butanediol. Generally speaking, results of these investigations have shown very little potential for adverse health effects from administration of even large quantities of 1,3-Butanediol to experimental animals or humans. A principle of toxicology is that if the body can handle a non-pharmacologically active compound using normal metabolic and excretion mechanisms then few compound-related adverse effects will occur. This principle is superbly illustrated in the case of 1,3-Butanediol, which can actually be used as a nutritional caloric source by mammals.

During an examination of the of the metabolism of various polyhydroxy compounds in rabbits, Gessner et al. (20) were unable to recover any recognizable metabolites of 1,3-Butanediol from the urine of treated animals. They postulated the 1,3-Butanediol was completely oxidized in the body by way of β-hydroxybutyrate. Kersters and DeLey (21) found that some species of bacteria oxidize 1,3-Butanediol using a soluble dehydrogenase. Tate et al (22) investigated the metabolic fate of 1,3-Butanediol in the rat and concluded that alcohol dehydrogenase (EC 1.1.1.1) catalyses the initial step in metabolism of 1,3-Butanediol to β-hydroxybutyraldehyde which is rapidly oxidized to β-hydroxybutyrate by aldehyde dehydrogenase. Subsequent metabolic steps to acetoacetate and acetyl CoA followed by entry of acetyl CoA into the tricarboxylic-acid cycle to produce carbon dioxide and reducing equivalents (that are converted to ATP by the electron transport chain) are well known biochemical pathways in mammals (23). Acetyl CoA is a central intermediate metabolite that can also be converted to sterols and fatty acids.

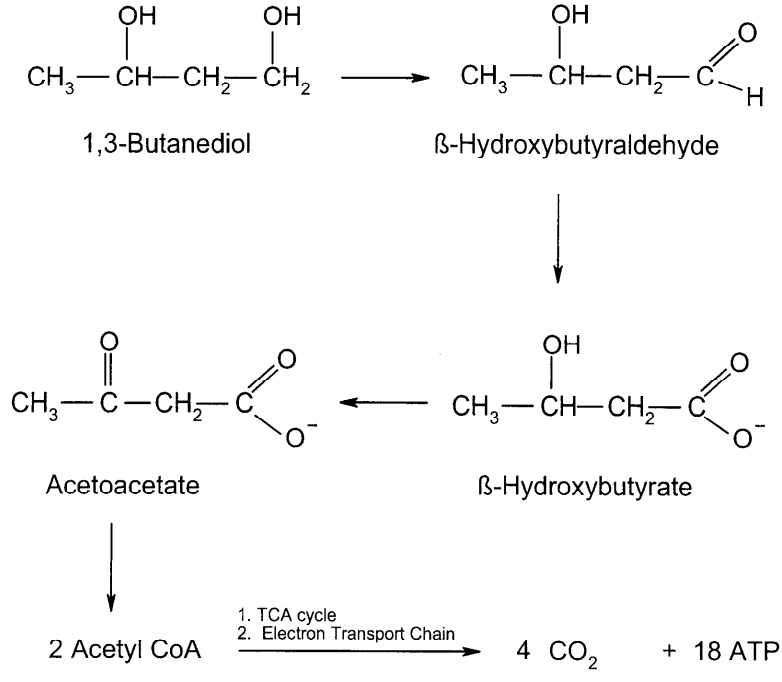


Figure 1: The mammalian metabolism of 1,3-Butanediol

From the established metabolic pathways it can be seen that 1,3-Butanediol is actually a reasonably good mammalian nutritional energy source. It has, in fact, been investigated as a "synthetic" food in cows, goats and humans with no adverse effects being reported. Discussion of the subject formed a symposium titled "Synthetic Food Additives as a Source of Calories: 1,3-Butanediol" at the 58th Annual Meeting of the Federation of American Societies for Experimental Biology in 1974.

Antidote for Ethylene Glycol Poisoning

In a 1992 report (24), the application of 1,3-Butanediol as an antidote for ethylene glycol intoxication was investigated by comparing it with ethanol, which is the standard therapy for ethylene glycol intoxication. The principle involved in the treatment is to inhibit the conversion of ethylene glycol to glyoxal, a process catalyzed by alcohol dehydrogenase (ADH). Studies had indicated that 1,3-butylene glycol (BG) binds to ADH more efficiently than EG and is less toxic orally than ethylene glycol or ethanol. In this study, male rats were divided into 5 groups of 6 animals each. Groups received by oral gavage either a single dose of ethylene glycol (32 mmole/kg), 1,3-Butanediol (39 mmole/kg, 3500 mg/kg) initially and every 6 hours up to 72 hours, ethanol (39 mmole/kg) initially and every 6 hours up to 72 hours, or ethylene glycol initially and then either 1,3-Butanediol or ethanol every 6 h up to 72 h. Administration of ethanol produced hepatotoxicity and pulmonary pathology as indicated by changes in clinical chemistry, urinalysis, and histopathology, while administration of 1,3-Butanediol alone did not. Neither ethanol nor 1,3-Butanediol produced any apparent nephrotoxicity. Ethanol produced ataxia, lethargy and central nervous system depression while 1,3-Butanediol did not. 1,3-Butanediol produced a higher concentration of urinary ethylene glycol indicating a better inhibition of ethylene glycol metabolism by ADH. Ethanol produced a higher EG blood concentration than BG. The higher EG blood concentration after ethanol administration may be partially attributed to dehydration and a decreased urine output as well as inhibition of ADH metabolism. Ethanol produced mortality in all animals prior to 72 hours. The ethylene glycol /ethanol combination produced mortality more quickly due to additive toxicity of the combination. Lack of any significant toxicity produced by 1,3-Butanediol and the production of significant toxicities by ethanol indicates that 1,3-Butanediol is potentially a better antidote than ethanol. Although this study was a not standard evaluation of toxicity, it serves to demonstrate the low toxicity of 1,3-Butanediol, which was administered at a dose of 3500 mg/kg every 6 hours for a period of 72 hours without producing significant toxicity. Furthermore, it confirms earlier observations that ADH is the initial enzyme involved in the metabolism of 1,3-Butanediol.

Acute Toxicity

Oral Exposure

Multiple determinations of the oral LD_{50} of 1,3-Butanediol were located in the open literature. These are elaborated in the table giving the LD_{50} value and the year of publication. One (Smyth et al. 1951) is written from

the original literature as a robust summary giving what details were available in that publication. Although these older literature studies lack extensive experimental details, they generally have good reliability regarding the major findings. In this case, there are a total of three rats studies, a mouse study and a guinea pig study all providing similar results. The existing older studies, the known low repeated dose toxicity, the established metabolic route and the structural similarity to other low toxicity materials combine to provide high confidence that the rat oral LD_{50} is far in excess of the maximum dose of 2000 mg/kg, recommended as the limit of a modern acute toxicity test.

Acute Oral Toxicity Studies			
Author	**Species**	**LD_{50} (mg/kg)**	**Year of pub (ref)**
Symth H.F. Jr. et al.	Rat	22800	1951 (25)
Symth H.F. Jr. et al.	Rat	18610	1941 (26)
Loeser, A	Rat	18610-30000*	1949 (27)
Wenzel & Koff	Mouse	12980	1956 (28)
Symth H.F. Jr. et al.	Guinea pig	11500	1941 (26)

* Also includes two Symth studies in range of values

Inhalation Exposure

It has been reported that there were no deaths when rats were exposed to saturated vapor of 1,3-Butanediol for 8 hours (25). The actual concentration was not measured but based on the vapor pressure of 0.08 hPa the vapor concentration is calculated to be in the range of 80 ppm.

Dermal Exposure

No studies of the acute dermal toxicity of 1,3-Butanediol were found. Studies on the irritation of this material show that small quantities do not result in mortality (29).

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints for acute toxicity. Although the available studies do not meet the requirements of the current OECD guidelines, the weight of evidence shows that the oral toxicity is very low. The conduct of additional studies would not add significantly to our understanding of this material's toxicity.

Repeat Dose Toxicity

Oral Exposure

Repeated-dose studies are available for two species. In a two-year feeding study in rats at 0, 1, 3 or 10% in feed, animals did not show any adverse effects related to treatment. The study used 30 rats of each sex per dose group and 60 rats of each sex in the controls. There was an interim sacrifice after 52 weeks of administration. Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment at levels up to 10% in feed (30).

A two-year study in beagle dogs using dosed feed at 0, 0.5, 1 or 3% 1,3-Butanediol is also reported in the literature. In this study, 4 dogs of each sex per group were exposed to test substance. There was an interim sacrifice after 52 weeks of administration. Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment at levels up to 3% in feed (30).

Eight-weeks dietary exposure of rats to 0, 5, 10, 20, 30 or 40% 1,3-Butanediol in the diet did not produce any signs of toxicity in a study reported in 1954 by Schlüssel (31).

A subchronic dosed feed study in dogs at 0, 3000, 6000, 9000 or 12000 mg/kg-day was conducted using groups of four dogs of each sex per dose level (32). In this study, reduction in body weight gain was observed at 9,000 and 12,000 mg/kg-day and was accompanied by organ weight, blood biochemistry, hematology, and behavioral changes. The treatment-related hematological changes were restricted to increases in platelet counts in the top two doses and an increased level of methemoglobin at only the high dose level. Biochemistry changes consisted of an increase in SGPT at the two highest doses, increased SGOT in the top dose group at 6-weeks but not at 13 weeks, and a dose-related increase in free fatty acids that was statistically significant only at the high dose. Relative organ weights of liver, kidney, brain, adrenals and lung were increased and relative weights of thymus and spleen were decreased at the top dose. At 9,000 mg/kg-day liver and kidney weights were increased. There were no pathological findings correlating with this upon either gross or microscopic examination. The most striking behavioral effect was epileptic-like seizures starting in the third week of the study in a high-dose animal. After the initial seizure, the number of dogs with seizures and the frequency of seizures increased with time affecting both males and females of the two highest-dose groups. Idiopathic epilepsy is known to occur in the colony of dogs used in this study; however, the seizures were dose-related. The 6000-mg/kg level was a NOAEL. Although the seizures were apparently dose related, they might have been secondary to metabolic alterations (e.g. reduced blood glucose levels) affecting CNS function in this colony of dogs with a predisposition to idiopathic epilepsy.

Oral Exposure, Nutritional Studies

In the early 1950s, research was conducted in Germany on synthetic calorie sources. Based on these initial investigations several groups have conducted extensive experiments in development of new synthetic sources of dietary calories for animals and man. 1,3-Butanediol was selected as the most promising "high-energy metabolite" and has been the subject of intensive study. Among these, the following studies reveal toxicologically relevant information regarding repeated dose exposure.

Rosmos et al. (33) looked at the effects of 1,3-Butanediol on hepatic fatty acid synthesis and metabolite levels in the rat. Groups of 10 male Sprague-Dawley rats were fed a basal diet containing 66.1% glucose, sucrose or the isocaloric equivalent of 1,3-Butanediol at 18% or 36% of the carbohydrate energy (1,3-Butanediol has an energy value of 6.5 kcal/g) for 23 days. A separate group of rats was given an i.p. injection of 800 mg 1,3-Butanediol. In vitro studies, using liver slices, were also performed with 10 mM 1,3-Butanediol as substrate.

Biochemical analyses indicated the plasma levels of glucose and triglycerides were significantly ($p < 0.05$) decreased in rats fed 1,3-Butanediol. Acute administration of 1,3-Butanediol to rats, on the other hand, increased the plasma levels of glucose. Free fatty acid plasma levels were not affected by single-dose administration of 1,3-Butanediol. Hepatic free fatty acid synthesis, however, was significantly ($P < 0.05$) decreased. Chronic administration of 1,3-Butanediol increased the liver levels of ß-hydroxybutyrate and acetoacetate. In vitro studies showed that 1,3-Butanediol decreased the conversion of glucose to free fatty acids in the liver without affecting the conversion of acetate to free fatty acids. It was speculated that 1,3-Butanediol may inhibit conversion of glucose to acetyl CoA. *In vitro*, release of pyruvate from liver slices was diminished but lactate release was not. Fatty acid synthesis in adipose tissue was not altered by 1,3-Butanediol administration. Data showed that 1,3-Butanediol was metabolized to ß-hydroxybutyrate and acetoacetate by rat liver. The lactate/pyruvate ratio was significantly ($p < 0.05$) increased, indicating that a shift towards a more reduced redox state in the cytoplasm after exposure to 1,3-Butanediol.

In a study to determine if depression of central nervous system from chronic ingestion of an alcohol is related to changes in brain metabolites, Veech et al. (1974) fed three groups of 10 male CFN Wistar strain albino rats standard rat diet for two weeks at which time their body weight was 270 g. These animals were fasted for five days, and then were fed commercial liquid diet in which 47% of the total calories were substituted with appropriate amounts of glucose, ethanol, or 1,3-Butanediol for a period of 62 days. The caloric values of glucose, ethanol, and BD are 3.68, 6.93 and 6.0 kcal/g, respectively. After treatment, brains and blood were analyzed for various metabolites. Brain lactate was significantly ($p < 0.005$) decreased in 1,3-Butanediol fed rats, as compared to glucose-fed rats. Levels of malate, aspartate, dihydroxyacetone phosphate, glucose-6-phosphate, ammonium ion, or creatinine phosphate were not affected by 1,3-Butanediol treatment. Brain glucose, however, was decreased 8-fold in 1,3-Butanediol treated rats compared to glucose treatment. Citrate and glutamate levels were higher in 1,3-Butanediol-exposed rats. Feeding of 1,3-Butanediol decreased blood glucose from 4.95 to 2.91 µmol/ml and increased blood ketone bodies.

Rosmos et al. (34) fed groups of rats, pigs, and chicks high fat basal diet containing 1,3-Butanediol at 0 or 17-19% of the dietary carbohydrate energy. They reported that feeding of 1,3-Butanediol significantly decreased ($p < 0.05$) the synthesis of free fatty acids in the rat liver, but not in pig liver or chick liver. Free fatty acids synthesis in the adipose tissue was unchanged in all species tested. The blood level of ß-hydroxybutyrate, acetoacetate, plasma levels of glucose, and triglycerides were increased by 48%, 24%, 89%, and 65%, respectively, in the 1,3-Butanediol-fed rats, as compared to controls. The blood levels of ß-hydroxybutyrate and acetoacetate in pigs and chicks were elevated, while the plasma glucose levels remained unchanged. The fact that the weight gain in rats, pigs, and chicks was not affected by 1,3-Butanediol at up to 20% of their dietary carbohydrate energy requirement suggested that rats, pigs, and chicks were able to utilize 1,3-Butanediol without loss of body weight at these levels. Their data further confirmed that 1,3-Butanediol decreases hepatic fatty acid synthesis in the rat and that 1,3-Butanediol is metabolized to hydroxybutyrate and acetoacetate.

Tobin et al. (35) have shown in several studies using human volunteers that isocaloric substitution of 1,3-Butanediol for starch caused less negative nitrogen balance and lower levels of blood glucose. In the fasting state and after glucose loading, however, concentrations of serum insulin and growth hormone were significantly increased. In one study, 12 young men and women were allowed a diet that contained 15 g of 1,3-Butanediol. Blood from each individual was analyzed for urea, proteins, haematocrit, haemoglobin, white blood cells, differential count, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, glucose-hydroxybutyrate, acetoacetate, lactate, pyruvate, triglycerides, free fatty acids, cholesterol, sodium, potassium, chloride, zinc, magnesium, and calcium. The results showed that feeding humans 1,3-Butanediol caused a significant reduction of urinary excretion of nitrogen as compared to those fed diet containing starch only. 1,3-Butanediol did not affect fecal excretion of nitrogen. Blood glucose levels were significantly lower in 1,3-Butanediol fed subjects. Feeding of 1,3-Butanediol did not alter any other biochemical, clinical, or haematological parameters. In another study by these investigators reported in the same communication, a group of 27 women were fed a diet containing 40 g 1,3-Butanediol per day without causing significant adverse effects.

Glucose tolerance tests conducted in a separate group of 10 men and women fed 1,3-Butanediol equivalent to 10% of the total energy intake for five days, showed no differences in levels of blood glucose during both glucose loading and fasting states. This suggests that humans can utilize 1,3-Butanediol at up to 10% of their total caloric intake without any adverse effects, with the exception that it may produce a hypoglycemic effect in some individuals (35).

Recommendation: No additional studies are recommended. The available data fill the HPV required endpoints for repeated-dose toxicity. The nutritional studies supply evidence that 1,3-Butanediol is metabolized by animals and by man as a dietary source of energy.

Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, adequate *in vivo* tests have been conducted that cover both of these two endpoints and, in addition, a 2-year study has indicated a lack of carcinogenic activity. Furthermore, this material is in a class of compounds without genotoxicity alerts.

Genetic Toxicology in vitro

In vitro tests of genetic toxicity for 1,3-Butanediol were not located. OECD 471 and 472 guideline studies were negative for the isomer, and close analog, 1,4-butanediol (see robust summaries, 36). Simple glycols, as a class, are not known to be genotoxic. There are two robust *in vivo* genotoxicity studies of this material. In addition, 1,3-Butanediol is rapidly metabolized in the body to β-hydroxybutyrate, which is a normal product of mammalian metabolism and not considered genotoxic.

Genetic Toxicology in vivo

Mammalian genotoxicity was assessed *in vivo* using both the dominant-lethal test in rats (males exposed for 13 weeks to 1,3-Butanediol at 0, 5, 10 or 24% by weight in the diet) and *in vivo* cytogenetics in rats, in which rat bone marrow cells were examined after multigenerational exposure from three different generations exposed continually to test substance at 0, 5, 10 or 24% by weight in the diet, were examined for cytogenetic abnormalities (37). No effect on fecundity, fetal or gestational parameters were observed in the dominant lethal assay and the mutagenic index (resorptions as a percentage of implant sites) showed no trend with increasing dose of test substance in the diet. In the cytogenetic analysis, the frequency of occurrence of abnormal cells was found to be within the normal range for the F1A, F2A and F3A animals in this multigenerational study. No specific abnormalities were consistently observed in any dosed group and no dose-related effects were noted. Thus, neither of these studies produced results indicative of genotoxic activity of 1,3-Butanediol.

Recommendation: The SIDS requirement for genetic testing has been met as assays sensitive to both point mutation and to clastogenic effects have been conducted using an acceptable protocol. No additional testing is recommended.

Reproductive Toxicity

1,3-Butanediol has been subjected to a multigenerational study in which groups of 25 males and 25 female rats were mated for four successive generations with continuous exposure to 0, 5, 10, or 24% (approximately 0, 2500, 5000, or 12,000 mg/kg-day) test material in the diet. In one part of the study, F1 animals were mated for five cycles. In this part there, was a gradual decrease in the pregnancy rate at the high dose with no pups being produced after the fifth mating. Although the investigators suggested that this might be due to a decrease in male fertility associated with growth suppression, no substantiating evidence was obtained from histopathological examination of the gonadal tissues. For the other three generations of mothers (who generally underwent two mating cycles) and pups, all reproductive parameters were comparable among all groups.

Recommendation: No additional testing is required as the available data are sufficient to assess the reproductive toxicity of this material.

Developmental Toxicity

A developmental toxicity study was conducted as part of the multigeneration study of Hess et al. (see robust summary) (37). In this study, it was concluded that there were no definitive dose-related teratological findings in either soft or skeletal tissue. Fetotoxicity (e.g., delayed ossification of sternebrae) was noted at dietary levels of 10 and 24%. Because maternal toxicity parameters were not reported for the developmental toxicity portion of the study, examination of body-weight data reported for the other generations was used in the robust summary to assess maternal toxicity. The data suggests that the high dose levels do not significantly affect body-weigh gain in non-pregnant females; however, high-dose males gained less body weight. It is clear from other studies (cited in the robust summary for the Hess developmental toxicity study) that the dietary levels associated with fetotoxicity are also associated with significant metabolic disturbances due to the nutritional value of 1,3-Butanediol. Although the fetotoxicity was not clearly associated with maternal toxicity, what is clear is that these dose levels cause marked metabolic alterations, which could result in fetotoxicity. In conclusion, based on the metabolic disturbances, the exceedingly high dose level and the relative minimal fetotoxicity, 1,3-Butanediol is considered to have little or no activity as a developmental toxin.

Other investigators have shown metabolic disturbances in rats fed levels of 1,3-Butanediol in the range of the mid-dose level of this developmental toxicity study. For example, Rosmos et al. (34) reported that rats fed 17-19% of their carbohydrate requirement as 1,3-Butanediol had significantly decreased synthesis of free fatty acids in the liver and increased blood levels of beta-hydroxybutyrate (48%), acetoacetate (24%), plasma glucose (89%) and plasma triglycerides (65%). As these significant metabolic effects appear to occur at dose levels in the same range as the mid-dose of this developmental study and, as it is not known how this altered maternal metabolic profiles affects the conceptus, it is possible that the developmental delays (reduced ossification) are a direct result of the altered nutrient supply and not a direct effect of the test substance.

Another study was reported in 1986 by Mankes et al, (38) who dosed pregnant Long-Evans rats with 0, 706, 4206 or 7060 mg/kg-bw from 6 to 15 of gestation. These investigators reported that the high dose was associated with selective fetotoxicity of male pups not contiguous to a female pup. No malformations were reported at any dose level. As in the other developmental toxicity studies, this high-dose level is probably associated with significant metabolic alterations, yet only minor fetotoxicity was produced.

These studies are also supported by an investigation by Dysma (39), who reported that 1,3-Butanediol is without adverse reproductive or teratogenic effects in rats, dogs or rabbits.

Recommendation: No additional testing is required as the available data are sufficient to assess the developmental toxicity of this material.

Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, the available information fills all of the requirements for physicochemical parameters, environmental fate, and toxicity information. No additional testing is recommended.

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AR201-14133B

Robust Summaries

1,3-Butanediol
CASNO 107-88-0

I U C L I D
Data Set

Existing Chemical	:	ID: 107-88-0
Memo	:	HPV
CAS No.	:	107-88-0
EINECS Name	:	butane-1,3-diol
EC No.	:	203-529-7
Molecular Weight	:	90.12
Structural Formula	:	CH3CHOHCH2CH2OH
Molecular Formula	:	C4H10O2

Producer related part

Company	:	Celanese Ltd
Creation date	:	30.10.2001

Substance related part

Company	:	Celanese Ltd
Creation date	:	30.10.2001
Status	:	
Memo	:	
Printing date	:	16.12.2002
Revision date	:	
Date of last update	:	16.12.2002
Number of pages	:	27
Chapter (profile)	:	Chapter: 1.0.1, 1.2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6.1, 3.1.1, 3.1.2, 3.3.1, 3.3.2, 4.1, 4.2, 4.3, 4.4, 5.1.1, 5.1.2, 5.1.3, 5.4, 5.5, 5.6, 5.8.1, 5.8.2
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	other:
Name	:	
Contact person	:	
Date	:	
Street	:	
Town	:	
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

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16.12.2002

1.2 SYNONYMS AND TRADENAMES

2.1 MELTING POINT

Value : = -77 °C

Remark : Handbook Data
Reliability : (2) valid with restrictions
Handbook values are assigned a reliability of 2

24.09.2002 (23)

2.2 BOILING POINT

Value : = 207.5 °C at 1013 hPa

Remark : Also listed as 207.5 C in Merck Index (Thirteenth Edition) and in manufacturer's product description sheet.
Reliability : (2) valid with restrictions
Handbook values are assigned a reliability of 2

27.11.2001 (23)

2.3 DENSITY

Type : density
Value : = 1.0059 g/cm³ at 20 °C

Remark : Handbook Value
Reliability : (2) valid with restrictions
Handbook values are assigned a reliability of 2

24.09.2002 (27)

2.4 VAPOUR PRESSURE

Value : = .08 hPa at 20 °C

Remark : Converted from 0.06 mm Hg as listed in handbook
Handbook Data
Test substance : 1,3-Butylene glycol (CASNO 107-88-0)
Reliability : (2) valid with restrictions
Handbook values are assigned 2

06.11.2002 (26)

Value : = .027 hPa at 25 °C

Remark : Handbook Value
Reliability : (2) valid with restrictions
Published value from secondary literature

24.09.2002 (6)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	= -.29 at °C
pH value	:	
Method	:	other (calculated)
Year	:	2001
GLP	:	
Test substance	:	
Reliability	:	(2) valid with restrictions Calculated by an acceptable method

26.11.2001 (54)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	miscible
Stable	:	
Reliability	:	(2) valid with restrictions Handbook value
Flag	:	Critical study for SIDS endpoint

24.09.2002 (33)

Solubility in	:	Water
Value	:	at °C
pH value	:	= 6 - 7
concentration	:	1 vol% at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	miscible
Stable	:	
Reliability	:	(2) valid with restrictions 2 Handbook Value

24.09.2002 (21) (50)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm³
Rate constant	:	= .0000000000142 cm³/(molecule*sec)
Degradation	:	= 50 % after .8 day(s)
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	
Test substance	:	

Method : Calculated using AOP version 1.90. Based on 12-hour day and the current EPA default of 1,500,000 hydroxyl radicals per cc.

Remark :

```
AOP Program (v1.90) Results:
============================
SMILES : CC(O)CCO
CHEM   : 1,3-Butanediol
MOL FOR: C4 H10 O2
MOL WT : 90.12
---------- SUMMARY (AOP v1.90): HYDROXYL RADICALS --------
Hydrogen Abstraction       =  13.9529 E-12 cm3/molecule-sec
Reaction with N, S and -OH =   0.2800 E-12 cm3/molecule-sec
Addition to Triple Bonds   =   0.0000 E-12 cm3/molecule-sec
Addition to Olefinic Bonds =   0.0000 E-12 cm3/molecule-sec
Addition to Aromatic Rings =   0.0000 E-12 cm3/molecule-sec
Addition to Fused Rings    =   0.0000 E-12 cm3/molecule-sec

 OVERALL OH Rate Constant =  14.2329 E-12 cm3/molecule-sec
   HALF-LIFE =     0.751 Days (12-hr day; 1.5E6 OH/cm3)
   HALF-LIFE =     9.018 Hrs
```

Reliability : (2) valid with restrictions
Calculated by an acceptable method

16.12.2002 (2)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Degradation	:	< 1 % after 1 year at pH and °C
Deg. product	:	
Method	:	
Year	:	2001
GLP	:	
Test substance	:	

Remark : Glycols of this type are considered resistant to hydrolysis

as they contain no hydrolysable group. Experience in the synthesis and use of this material is also consistent with it being resistant to hydrolysis.

Source : Celanese Ltd
Reliability : (2) valid with restrictions
Estimated by an accepted method

26.11.2001 (28)

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type :
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: calculated
Year :

Remark : The Henry's Law constant indicates that this compound is essentially non-volatile from water.
Result : Henry's Law constant: 0.00000023 Pa x m3 x mol-1
Source : Hoechst Celanese NV Rotterdam
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

31.05.1995 (20) (29)

3.3.2 DISTRIBUTION

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level III
Year : 2001

Method : Calculated using MacKay level III model in EPIWIN 3.05 using highest measured vapour pressure value.
Result : Level III Fugacity Model (Full-Output):

==========

Chem Name : 1,3-Butanediol
Molecular Wt: 90.12
Henry's LC : 2.3e-007 atm-m3/mole (Henrywin program)
Vapor Press : 0.06 mm Hg (user-entered)
Log Kow : -0.29 (Kowwin program)
Soil Koc : 0.21 (calc by model)

	Concent. (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.96	18	1000
Water	49.7	208	1000
Soil	47.3	208	1000
Sediment	0.074	832	0

	Fugacity	Reaction	Advection

	(atm)	(percent)	(percent)
Air	4.66e-011	22	5.74
Water	3.69e-012	32.1	9.63
Soil	1.28e-010	30.5	0
Sediment	2.75e-012	0.012	0.000288

Persistence Time: 194 hr
Reaction Time: 229 hr
Advection Time: 1.26e+003 hr
Percent Reacted: 84.6
Percent Advected: 15.4

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 18.04
Water: 208.1
Soil: 208.1
Sediment: 832.3
Biowin est: 3.320 (days-weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Reliability : (2) valid with restrictions
26.11.2001

(10)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other: Estimate
Species	:	other
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 9484 calculated
Method	:	other: calculated
Year	:	2001
GLP	:	
Test substance	:	

Method :

The fish LC50 value was estimated using the V0.99 ECOSAR Classes program found in EPIWIN version 3.05. The following equation for neutral organics was used for the calculation:

Log LC50 = -0.94 log Kow + 1.75

The LC50 is in millimoles per liter (mM/L); and the equation is based on the fish toxicity of known neutral organic compounds (N = 60 with the Coefficient of Determination (R2) = 0.942.)

The log Kow was estimated to be -0.29 using the KOWWIN (ver 1.66) program found in EPIWIN version 3.05.

This equation is considered appropriate for uncharged alcohols with log Kow vlaues less than 5.

Remark :

The ECOSAR prediction for green algae EC50 was found to be in accord with the experimental value. This supports the use of ECOSAR for 1,3-butanediol
Estimates using a reliable method are assigned a reliability of 2. In this case, since the estimated LD50 is high, and similar alcohols have fish LC50 in this same range the confidence that the LC50 is large (i.e above 100 mg/L) is high.

Conclusion :

The 96 hour LC50 of 1,3-Butylene glycol for freshwater fish is estimated to be approximately 9,500 mg/L. This material is considered to present little hazard to fish.

Reliability : (2) valid with restrictions
26.11.2001

(9)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	other
Species	:	other
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 8684 calculated
Method	:	other: calculated
Year	:	2001

GLP	:	
Test substance	:	
Method	:	The daphnia LC50 value was estimated using the V0.99 ECOSAR Classes program found in EPIWIN version 3.05. The following equation for neutral organics was used for the calculation: Log LC50 = 1.72 - 0.91 log Kow The LC50 is in millimoles per liter (mM/L); and the equation is based on the daphnia toxicity of known neutral organic compounds (N = 19 with the Coefficient of Determination (R2) = 0.992.) The log Kow was estimated to be -0.29 using the KOWWIN (ver 1.66) program found in EPIWIN version 3.05. This equation is considered appropriate for uncharged alcohols with log Kow values less than 5.
Remark	:	The ECOSAR prediction for green algae EC50 was found to be in accord with the experimental value. This supports the use of ECOSAR for 1,3-butanediol Estimates using a reliable method are assigned a reliability of 2. In this case, since the estimated ED50 is high, and similar alcohols have daphnia EC50s in this same range the confidence that the EC50 is large (i.e above 100 mg/L) is high.
Conclusion	:	The 48-hour LC50 of 1,3-Butylene glycol for daphnia fish is estimated to be approximately 8,700 mg/L. This material is considered to present little hazard to aquatic invertebrates.
Reliability	:	(2) valid with restrictions

26.11.2001 (9)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	> 1070 measured/nominal
EC50	:	> 1070 measured/nominal
Limit test	:	
Analytical monitoring	:	yes
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	2000
GLP	:	yes
Test substance	:	
Method	:	The study was conducted in accordance with EC Methods for Determination of Ecotoxicity Annex to Directive 92/69/EEC (O.J. No. L383A, 29.12.92) Part C, Method 3 "Algal Inhibition Test" and the OECD Guideline for Testing of

Chemicals No. 201 "Alga, Growth Inhibition Test".

CULTURE MEDIUM:
Sterile algal nutrient medium as recommended in Official Journal No. L383A Part C.3 and OECD Procedure 201 (Appendix 1

PREPARATION OF TEST SUBSTANCE DILUTIONS:
A concentrated, aqueous stock was prepared at a nominal concentration of 10 g/L by adding the test substance (1 g) to a volumetric flask (100 ml) and making up to volume with sterile culture medium. An aliquot (10 ml) of this stock was added to each vessel containing inoculated culture medium.

ANALYTICAL DETERMINATIONS:
The test concentration was measured using a GLC method of analysis. At the start of the definitive test, four samples (20 ml) were taken from additional flasks containing the freshly-prepared control and test medium; after 72 hours, the contents of the replicate flasks for each group were pooled and further samples were taken for analysis. Additional samples were also taken from flasks containing 1,3-Butylene glycol at 1000 mg/l but with no algal cells, in order to obtain information on the extent of adsorption/absorption of the test substance by the algal cells. On each occasion, two of the samples were analyzed immediately and the others were stored in a refrigerator in case further analysis was required.

TEST CONDITIONS
Test vessels (250 ml conical flasks), each containing algal medium (50 ml), were loosely stoppered with cotton wool, covered with aluminium foil which was secured by autoclave tape and sterilised by autoclaving. Following the addition of algal inoculum (40 ml) and the test substance (as a 10 ml aliquot of an aqueous stock), the initial cell density in each flask was approximately 1,000,000 cells/ml.Each flask was then loosely plugged with non-absorbent cotton wool. The cultures were incubated, without renewal of medium, for 72 hours under continuous illumination of approximately 9140 lux provided by 5 x 30 W "cool white" 1 meter fluorescent tubes. The temperature was maintained at 23 ± 2°C.

Samples were taken from control and test flasks at 24, 48 and 72 hours and the cell densities measured using a haemacytometer. The estimate of cell numbers in each sample was based on the mean of four or eight consecutive counts depending on the cell density of the cultures.

Remark : No significant deviations from the protocol occurred.

Result :

The intended level of 1,3-Butylene glycol in unfiltered samples of the test culture was adequately achieved and maintained. Mean measured concentrations ranged from 1.06 g/L at the start of the test to 1.08 g/L after 72 hours. The overall mean measured level of 1,3-Butylene glycol was 1.07 g/L.

After 72 hours, analysis of an unfiltered sample of medium containing 1,3-Butylene glycol which had been incubated without algal cells gave similar results to test medium incubated in the presence of algal cells; this indicates that the presence of algal cells had not affected the stability of 1,3-Butylene glycol under the test conditions.

Individual cell densities for each culture and the mean values are given in the table below.

Measured conc. (mg/L)	Replicate number	Cell Density (1000s) 24-hr	48-hr	72-hr
N.D.	R1	10.8	86.9	245
	R2	14.6	75.0	339
	R3	13.9	86.6	351
	R4	11.1	78.8	393
	R5	10.5	84.3	323
	R7	14.0	85.3	306
Mean		12.5	82.8	326
1070	R1	12.1	86.5	312
1070	R2	11.6	99.1	408
1070	R3	12.1	95.5	416
1070	R4	10.4	104	344
1070	R5	10.5	87.0	340
1070	R6	12.5	101	344
Mean		11.5	95.5	361

N.D = not detected, these were controls

Test substance : 1,3-Butylene glycol
CASNO 107-88-0
Purity 99.8%

Conclusion : 1,3-Butylene glycol was not inhibitory to the growth of Selenastrum capricornutum cultures when dissolved in algal nutrient medium at a mean measured level of 1070 mg/L.
The 72-hour median effect concentrations for inhibition of growth were not identified but must be greater than 1070 mg/L.
The no-observed effect concentration (NOEL) for inhibition of growth was > 1070 mg/l

Reliability : (1) valid without restriction
16.12.2002

(1)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	= 22800 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1951
GLP	:	no
Test substance	:	no data
Method	:	Single-dose administration to non-fasted animals. Animals were observed for 14 days after dosing. Group size not specified in publication. Method may be provided in a references paper. LD50 determined by the method of Thompson using +- 1.96 standard deviations as the limits.
Result	:	The oral single-dose LD50 for non-fasted rats was determined to be 22.8 g/kg, with a range (plus or minus 1.96 standard deviations) of 21.8 to 23.9 g/kg.
Test substance	:	1,3-Butylene glycol (CASNO 107-88-0)
Reliability	:	(2) valid with restrictions Reliability 2, although few details were given the investigator's work is considered reliable.
Flag	:	Critical study for SIDS endpoint

06.11.2002 (46)

Type	:	LD50
Value	:	= 18610 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1941
GLP	:	no data
Test substance	:	no data
Test substance	:	1,3-Butylene glycol (CASNO 107-88-0)
Reliability	:	(4) not assignable Considered 4 since taken from secondary literature

07.11.2002 (45)

Type	:	LD50
Value	:	= 12980 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	

Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1956
GLP	:	no data
Test substance	:	no data
Test substance	:	1,3-Butylene glycol (CASNO 107-88-0)
Reliability	:	(4) not assignable Considered 4 since taken from secondary literature

07.11.2002 (53)

Type	:	LD50
Value	:	= 11500 mg/kg bw
Species	:	guinea pig
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other: no data
Year	:	1941
GLP	:	no data
Test substance	:	no data
Test substance	:	1,3-Butylene glycol (CASNO 107-88-0)
Reliability	:	(4) not assignable Considered 4 since taken from secondary literature

07.11.2002 (47)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other: Inhalation Hazard Test
Value	:	
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	8 hour(s)
Method	:	other: no data
Year	:	1951
GLP	:	no
Test substance	:	no data
Remark	:	Based on a vapor pressure of 0.08 hPa, the saturated vapor concentration is in the range of 60 ppm.
Result	:	No deaths from exposure to saturated vapor for 8 hours (concentration not specified).
Test substance	:	1,3-Butylene glycol (CASNO 107-88-0)
Reliability	:	(2) valid with restrictions Reliability 2, although few details were given the investigator's work is considered reliable.

06.11.2002 (46)

5.1.3 ACUTE DERMAL TOXICITY

5.4 REPEATED DOSE TOXICITY

Type	:	Chronic
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	1.0, 3.0 10.0%
Control group	:	yes, concurrent no treatment
NOAEL	:	= 10 - 0 %
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	other TS: purity: 99.98%

Method :

Dosing was conducted by incorporating test material into food at 1, 3 or 10% by weight

Animals were weanling Sprague-Dawley rats

Dose group size was 30 animals of each sex

Control group size was 60 animals of each sex

Body weights were reported for animals at 0, 4, 20 and 52 weeks. Other body weights were not included in the publication.

Blood samples taken from representative animals in each group at six intervals during the study. Tests run were CBC, hematocrit and hemoglobin.

Pooled urine samples were taken from representative animals in each group at six intervals during the study. Tests run were specific gravity, pH, protein, sugar, acetone, urobilinogen and occult blood.

After one year, ten animals from each group were sacrificed and necropsied. Representative organ weights were recorded (data for liver, kidney, adrenal, thyroid and testes are given in the report from animals surviving for 2 years) and 17 organs were submitted for histopathologic evaluation. At the end of two years the same procedure was followed with all surviving animals

Remark : Feed consumption data not given in publication; however, as the body weight gains for all dosed groups were similar to controls, this is not considered a major deficiency.

Result :
Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment
Mean Body Weights at 52 weeks were:
\\controls, 1%, 3% and 10%,
Males \\565g, 560g, 551g, 578g
Females \\347g, 320g, 347g, 370g

Reliability : (2) valid with restrictions
Study conducted prior to GLP implementation. Publication has adequate details for assessment of quality.

Flag : Critical study for SIDS endpoint
06.11.2002 (37)

Type	:	Chronic
Species	:	dog
Sex	:	male/female
Strain	:	Beagle
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	daily
Post exposure period	:	none
Doses	:	0.5, 1.0, 3.0%
Control group	:	yes, concurrent no treatment
NOAEL	:	= 3 - 0 %
Method	:	other: no data
Year	:	1967
GLP	:	no data
Test substance	:	other TS: purity: 99.98%

Method :
Dosing was conducted by incorporating test material into food at 0.5, 1, or 3% by weight

Animals were 6-16 month old purebred beagles

Dose group size was 4 animals of each sex

Control group size was 4 animals of each sex

Body weights were reported for animals at 0, 4, 20 and 104 weeks. Other body weights were not included in the publication.

Blood samples taken from representative animals in each group at eight intervals during the study. Tests run were CBC, hematocrit, hemoglobin, sedimentation rate, BUN and bromosulphalein retention.

Pooled urine samples were taken from representative animals in each group at eight intervals during the study. Tests run were specific gravity, pH, protein, sugar, acetone, urobilinogen and occult blood.

After one year, two animals of each sex from each group were sacrificed and necropsied. Representative organ weights were recorded (data for liver, kidney, adrenal, thyroid and

testes are given in the report from animals surviving for 2 years) and 19 organs were submitted for histopathologic evaluation.

Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment

Result :

Mortality, body weight gain, blood parameters, urine parameters, organ weights, incidence of neoplasm, and organ histopathology were unaffected by the two-year treatment

Reliability : (2) valid with restrictions

Study conducted prior to GLP implementation. Publication has adequate details for assessment of quality

06.11.2002 (39)

Type : Sub-chronic
Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : oral feed
Exposure period : 13-weeks
Frequency of treatm. : daily
Post exposure period :
Doses : 0, 3000, 6000, 9000 and 12000 mg/kg-day
Control group : yes, concurrent no treatment
NOAEL : = 6000 mg/kg
LOAEL : = 9000 mg/kg
Method :
Year : 1978
GLP : no data
Test substance :

Method : The test substance was thoroughly mixed into a basal diet at levels providing an intake of 0, 3, 6, 9 or 12 g/kg body weight/ day. The diets were supplemented with an instant wheat product, glucose and soya bean oil in such a way that all diets were theoretically isocaloric. The diets were freshly prepared once a week and stored in closed containers at a temperature of 10-150C. The dogs were fed a restricted portion of food twice daily. The amount of food/kg body weight/day was either 50 or 40 g on different days, but was equal for the different dogs on one day.

The study was initiated with 20 male and 20 female purebred beagle dogs, about 7-8 weeks old. They were obtained from the colony maintained at the Central Institute for the Breeding of Laboratory Animals, CPB-TNO, Zeist, The Netherlands. The animals were divided into 5 groups (one control and 4 test groups) of four males and four females each, and individually housed in indoor kennels.

Conduct of the experiment:
Behavior and health of all dogs were checked daily.. Individual body weights were measured weekly. Individual food consumption was measured daily. Haematological investigations were carried out at the beginning and at weeks 2, 6 and 12 in all dogs. All blood samples were examined for: hemoglobin content, packed cell volume, methemoglobin content, erythrocyte fragility, erythrocytes count, leukocyte count, platelet

count, differential white blood cell count, reticulocyte count and Heinz bodies.

Blood clinical chemistry parameters were SGPT, SAP, total serum protein, serum albumin, fasting blood glucose, blood urea-N, triglycerides, B-hydroxybutryric acid, acetoacetic acid. plasma free fatty acids and lactate. Urine analyses, including appearance, specific gravity, pH, sugar, protein, occult blood, ketones and microscopic examination of the sediment were conducted upon all dogs at the beginning and at week 6 and 12. A liver-function test (bromosulphophthalein method) was carried out upon all dogs of the control and highest dose group at week 13. A kidney-function test (phenolred excretion method) was conducted upon all dogs of the control and highest dose group at week 13.

After 13 weeks, all surviving dogs were anaesthetized by intravenous administration of Nembutal followed by exsanguinations. A thorough necropsy was performed on each animal immediately after death. The following organs were weighed: heart, kidneys, liver, spleen, lungs, testicles/ovaries, pituitary, thyroids, adrenals and brain. Samples of these organs together with a wide range of other organs and tissues were fixed. Detailed microscopic examination was done on all dogs. H and E stained paraffin sections of the organs weighed and also of the following organs and tissues were examined: spinal cord, sciatic nerve, salivary glands, skeletal muscle, thoracic aorta, skin, tonsils, bladder, esophagus, stomach, duodenum, jejunum, ileum, caecum, colon, pancreas, trachea, circumanal glands, eyes, epididymis, prostate, uterus, gall bladder, tongue and thymus.

Remark :

Although the seizures were apparently dose related they may have been secondary to metabolic alterations (e.g. reduced blood glucose levels) affecting CNS function in this colony of dogs with a predisposition to idiopathic epilepsy.

Result :

Reduction in body weight gain was observed at 9,000 and 12,000 mg/kg-day and was accompanied by organ weight, blood biochemistry, hematology, and behavioral changes. The treatment-related hematological changes were restricted to increases in platelet counts in the top two doses and an increased level of methemoglobin at only the high dose level. Biochemistry changes consisted of an increase in SGPT at the two highest doses, increased SGOT in the top dose group at 6-weeks but not at 13 weeks, and a dose-related increase in free fatty acids that was statistically significant only at the high dose. Blood levels of free fatty acids, G-hydroxy butyric acid, acetoacetic acid and lactate increased with increasing feeding levels of BD. The excretion of phenol-red and bromosulphophthalein did not indicate impaired function of the liver or kidneys. Slight ketonuria was observed in dogs of the top-dose group at week 12. Small quantities of BD were recovered from feces of dogs fed 9 or 12 g BD/kg body weight/day.

Relative organ weights of liver, kidney, brain, adrenals and lung were increased and relative weights of thymus and spleen were decreased at the top dose. At 9,000 mg/kg-day liver and kidney weights were increased. There were no pathological findings correlating with this upon either gross or microscopic examination.

The most striking behavioral effect was epileptic-like seizures starting in the third week of the study in a high-dose animal. After the initial seizure the number of dogs with seizures and the frequency of seizures increased with

time affecting both males and females of the two highest-dose groups. Idiopathic epilepsy is known to occur in the colony of dogs used in this study; however, the seizures were dose-related. The 6000 mg/kg level was a NOAEL.

Test substance : 1,3-Butylene glycol 99.5 wt % min
Reliability : (1) valid without restriction
Well documented study

12.11.2002 (51)

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
System of testing :
Test concentration : 0, 313, 625, 1250 and 5000 mcg/plate, for both + and - S9
Cycotoxic concentr. : Greater than 5000 mcg/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year :
GLP : no data
Test substance : other TS

Method : OECD 471 and OECD 472
Remark : Bacterial strains used were S. typhimurium TA100, TA98, TA1535, TA1537 and E coli WP2 uvrA.
S9 was produced from rat liver induced with phenobarbital and 5,6-benzoflavone.
Toxicity to bacteria was not observed at 5000 mcg/plate in all five strains with or without a S9 mix.
Result : Negative
Test substance : 1,4-Butanediol (Isomer of 1,3-butanediol, purity 98.0%)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.11.2002 (3)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 13 weeks or longer
Doses : 5, 10, 24%
Result : negative
Method : other: no data
Year : 1981
GLP : no data
Test substance : no data

Method :
This in vivo cytogenetics test utilized FIA, F2A and F3A animals from a concurrent multigenerational study. At least two rats per sex per group, continuously dosed with test

substance at 0, 5, 10 or 24% by weight in the diet (semi-purified diet), were examined for cytogenetic analysis. Animals were sacrificed and bone marrow (femur) preparations were examined cytologically for treatment related aberrations in the chromosomal patterns. The selected rats were injected intraperitoneally with colchicine (1 mg/kg), 3-4 hours prior to sacrifice. Following dissection, the marrow was washed with 5 ml of Hank's balanced salts solution. The cells were centrifuged, washed repeatedly with fresh Hank's solution. The cells were then suspended in 6 ml of hypotonic fetal calf serum and incubated at 37 C for 20 minutes. The cells were fixed in a 3:1 mixture of methanol-glacial acetic acid at 4 C, overnight, before being coated on coverslips and stained with 2% aceto-orcein. The preparations were examined by phase-contrast microscopy at 900x magnification for aberrant chromosomes. One hundred to 250 metaphase cells were examined per group

Remark :

at least 2 animals/sex/group from the F1A, F2A and F3A generations of a reproduction study were examined.

Result :

The frequency of occurrence of abnormal cells was found to be within the normal range for the F1A, F2A and F3A animals in this multigenerational study. No specific abnormalities were consistently observed in any dosed group and no dose-related effects were noted.

Reliability : (2) valid with restrictions
04.11.2002 (15)

Type : Dominant lethal assay
Species : rat
Sex : male
Strain : Wistar
Route of admin. : oral feed
Exposure period : 13 weeks
Doses : 5, 10, 24%
Result :
Method : other: no data
Year : 1981
GLP : no data
Test substance :

Method :

This dominant lethal test utilized F1B male animals from a concurrent multigenerational study. Ten males per group were reared to maturity while being continuously dosed with test substance at 0, 5, 10 or 24% by weight in the diet (semi-purified diet). The sires and dams producing these males were dosed at the same levels throughout mating, gestation and lactation. Each male was housed individually in a mating cage and two virgin 100-day old untreated females were introduced and permitted to remain with a male for 7 days, this was repeated each week for eight consecutive weeks. After removal from the mating cage, each female was individually housed for an additional 7 days and then sacrificed for examination of the reproductive tract.

The numbers of implant and/or resorption sites and viable and dead fetuses were recorded. These data were used to calculate the mutagenic index according to the method of Epstein and Shafner

Remark :

Conducted as part of reproduction study; 10 mature F1B males per group were mated to virgin females each week for 8 consecutive weeks.

Study protocol was basically in accord with OECD 478. Slightly fewer males were treated and mated than recommended but the top dose level was higher than recommended, more total females were examined and the duration of dosing was longer than recommended. Overall, this appears to be a robust and well conducted study.

Result :

All males in the dose groups sired litters. The percentage of pregnancies as well as the percentage of viable fetuses per implant site were not significantly different between treatment and control groups. The mutagenic index (resorptions as a percentage of implant sites) showed no trend with increasing dose of test substance in the diet.

Mutagenic Index

Dose	Average over 8 weeks
0%	5.5 (1101 viable fetuses)
5%	6.1 (962 viable fetuses)
10%	4.3 (1389 viable fetuses)
24%	3.2 (1269 viable fetuses)

Conclusion : Material is negative in this genotoxicity assay
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
04.11.2002 (17)

5.8.1 TOXICITY TO FERTILITY

Type : other: five generation study
Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : See Remarks below
Frequency of treatm. : daily
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses : 5, 10, 24%
Control group : yes, concurrent no treatment
NOAEL parental : = 24 %
NOAEL F1 offspring : = 24 %
NOAEL F2 offspring : = 24 %
Method : other: no data

Year : 1981
GLP : no data
Test substance : no data

Method : All generations: 25 male and 25 female animals/group. Test substance was substituted for equal ammounts by weight of corn starch and dextrose.

Five successive mating cycles were achieved with the F1A rats over a period of 77 weeks.

Reproductive indices were calculated for each series of litters.

For F1A rats, which survived at least 66 weeks, the gonads and pituitary glands were examined microscopically

Result :

Reproduction and lactation parameters were comparative to controls for four of five generations of dams and pups. The pregnancy rate of F1A rats decreased during five successive mating cycles. Excluding this group, the viability of F2 generation pups revealed no significant differences between litters or between control and test groups. No reason for the decrease in fertility index in the fifth generation was determined; however, controls were also affected but to a lesser degee.

Fertility Index: (percent)

	Generation				
	F2A	F2B	F2C	F2D	F2E
Control	72	44	64	60	40
5%	80	44	76	60	16
10%	92	64	68	40	20
24%	76	52	44	28	00

Mean Body Weight Pups at Birth: (grams)

	Generation				
	F2A	F2B	F2C	F2D	F2E
Control	10.0	10.0	10.9	10.4	11.1
5%	9.6	10.5	10.5	10.6	13.0
10%	9.3	10.6	10.0	10.5	11.0
24%	10.6	10.4	11.0	11.6	---

No significant treatment-related effects were noted on examination of testes, ovaries, or pituitary glands.

Test substance : 1,3-Butylene glycol (CASNO 107-88-0)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.11.2002 (17)

Type : other: three generation study
Species : rat
Sex : male/female

Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	no data
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	20%
Control group	:	no data specified
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	no data

Result : No effect on fertility, litter size or number of live offspring, despite reduced weight gain in the parents of each generation.

06.11.2002 (8)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Long-Evans
Route of admin.	:	gavage
Exposure period	:	Day 6 to Day 15 gestation
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	706, 4236, 7060 mg/kg
Control group	:	yes, concurrent no treatment
NOAEL maternal tox.	:	= 7060 mg/kg bw
NOAEL teratogen.	:	= 7060 mg/kg bw
LOAEL Fetotoxicity	:	= 7060 mg/kg bw
NOAEL Fetotoxicity	:	= 4263 mg/kg bw
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	

Method :

Long-Evans rats (200-300 g), obtained from Blue Spruce Farms in Altamont, NY were mated to produce presumed-pregnant dams defined by the presence of sperm in the vaginal smear that was defined as day 0 of gestation. Presumed-pregnant dams were divided into four groups of 10 assigning animals to equalize bodyweights among groups.

Test material was administered daily by gavage from day 6 to day 15 of gestation, based on current bodyweights. The exposure levels were chosen as fractional doses (24, 14.4, and 2.4%) of the acute LD50 value for the test substance. The exposure period was, the so-called critical period of organogenesis. Dose levels were 0, 706, 4236 or 7060 mg/kg-day. Animals were observed daily for mortality or for signs of intoxication (lethargy, ataxia, activity in response to a light cage tap). Food

consumption was monitored by daily visual inspection of ground diet (Wayne Lab Blox) remaining in calibrated metal feed cups. All dams were overdosed with ether on day 20 of gestation, and fetuses were delivered by caesarean section. At necropsy on gestation day 20, total uterine weight, total litter weight, individual pup weights, crown-rump length, number of live pups, stillbirths and resorptions, implantation sites, sex distribution, and number of corpora lutea were recorded for each pregnancy.

All live pups were examined for gross malformations at birth. Soft tissue (internal) defects were evaluated by free-hand slicing and skeletal and cartilaginous variations were detected by alizarin red-S and alcian blue staining. Subjective fetal anomalies were judged as representing a marked deviation from normality according to standard criterion score sheets by blind observers. Live pups were classified according to contiguity with offspring of the same or opposite sex and analyses were conduced with reference to the treatment group and fetal subtype for bodyweight.

Remark :

STATISTICAL METHOD: All data generated in the course of the study were entered, archived, and statistically analyzed on pc. Statistical analyses of the data were performed using an interactive, disc-based software package (Crunch Interactive software, version 83.1, Crunch Software, Inc.), using the litter as the experimental unit. Parametric analysis of variance and Newman-Keuls posthoc analyses were used to compare maternal bodyweights, uterine weights, litter weights, pup weights, crown-rump lengths, corpora lutes, implantations, percent of males per litter, intrauterine deaths per litter, malformed pups per litter, and pup bodyweights by contiguity classification on an absolute and relative (percent of control) basis. Contingency table analyses (Chisquare and Fisher exact test) were applied to litters bearing malformed pups. Linear regression analysis of butanediol dose against pup bodyweight was performed.

Result :

Reproductive Parameters

	Control	High	Mid	Low
Pregnant	10	8	9	8
Gestation weight gain (%)	50	54	47	50
Dam weight gain (%)	25	28	23	25
Total litter weight(g)	39	38	36	44
Avg pup weight (g)	3.5	3.1	3.3	3.5
Avg pup size (crown-rump length, cm)	3.5	3.5	3.5	3.6
Corpora lutea/dam	11.6	12.1	11.2	11.9
Implants/dam	11.8	14.5	12.4	12.4
Litter size	11.2	11.9	10.9	12.0
Percent males/litter	36.3	44.8	56.0	41.7
In utero deaths/dam	0.6	2.6	1.6	1.9
Malformed pups/dam	1.6	3.0	2.7	2.1
Litters with malformed	7	6	7	5

The investigators reported: Maternal exposure to high doses of 1,3-butancdiol, during organogeneeis was associated with a significant decrease in offspring birthweights only at the highest (7060 mg/kg) dose. This birthweight depression selectively affected high-dose male offspring not contiguous in utero to a female sibling. Other pups were not

significantly affected by 7060 mg/kg of butancdiol.

"These findings indicate that in utero levels of sex steroids modulate the expression of earlier fetal damage at parturition by inhibiting (testosterone) or enhancing (estradiol) cellular repair by a mechanism as yet undefined. From these data it is concluded that intrauterine position with respect to contiguous siblings is an important factor in the expression of developmental toxicity at parturition."
Not teratogenic; fetotoxicity was evidenced by a dose-dependent decrease in offspring birthweights. Maternal sedation noted at mid and high doses.

Test substance : 1,3-Butylene glycol (CASNO 107-88-0), Reagent Grade, 98%
Reliability : (2) valid with restrictions
Published article, good details
Flag : Critical study for SIDS endpoint
05.11.2002 (30)

Species : rat
Sex : female
Strain : Wistar
Route of admin. : oral feed
Exposure period : day 0 to day 19 of gestation
Frequency of treatm. : daily
Duration of test :
Doses : 5, 10, 24%
Control group : yes, concurrent no treatment
NOAEL maternal tox. : %
NOAEL teratogen. : = 24 %
NOAEL Fetotoxicity : = 5 %
Method : other: no data
Year :
GLP : no data
Test substance : no data

Remark : 14-15 animals/group
Result :

Incidence of fetal skeletal abnormalities in F3B generation rats

Dietary level(%)	0	5	10	24
Fetuses exam	124	103	120	103
Sternebrae				
Incomplete ossif'	31	31	48*	65*
Scrambled	1	0	0	0
Bipartite	1	1	0	3
Extra	1	0	0	0
Missing	10	3	13	31*
Ribs				
More then 13	4	4	1	1
Vertebra				
Incomplete ossif'	4	1	1	2
Scoliosis	1	0	0	0
Skull				
Incomplete closure	9	0	3	10

Hyoid bone				
Missing	2	0	0	2
Reduced	0	0	0	1

Maternal toxicity parameters were not reported for the developmental toxicity portion of the study. Examination of body-weight data reported for the other generations suggests that the high dose does not significantly affect body-weigh gain in non-pregnant females. High-dose males gained less body weight.

Other investigators have shown metabolic disturbances in rats fed levels of 1,3-butanediol in the range of the mid-dose level of this developmental toxicity study. For example, Rosmos et al. (Federation Proc 34: 2186, 1975) reported that rats fed 17-19% of their carbohydrate requirement as 1,3-butanediol has significantly decreased synthesis of free fatty acids in the liver and increased blood levels of beta-hydroxybutyrate (48%), acetoacetate (24%), plasma glucose (89%) and plasma triglycerides (65%). As these significant metabolic effects appear to occur at dose levels in the same range as the mid-dose of this developmental study and, as it is not known how this altered maternal metabolic profiles affects the conceptus, it is possible that the developmental delays (reduced ossification) are a direct result of the altered nutrient supply and not a direct effect of the test substance.

For the above reasons, and because only limited fetotoxicity occurred at these extraordinary high dose levels, this material is not considered a specific developmental toxin.

Resorption and implantation data for F3B generation rats

Diet Level	Number Preg Female	# pups/liter Viable	Non-V	#/dam	Implants #/dam	Resorp Wt (g)	Pup
0	15	11.9	0	12.5	0.6	3.5	
5	15	10.1	0	10.4	0.3	4.0	
10	14	12.1	0	12.6	0.5	4.1	
24	14	10.9	0	11.4	0.5	3-4	

Conducted as part of reproduction study; no definitive dose-related teratological findings in either soft or skeletal tissue. Fetotoxicity(e.g., delayed ossification of sternebrae) noted at 10% and 24% doses.

Reliability : (2) valid with restrictions
Published article, good details

06.11.2002 (16)

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